Remarks

Claim 1 has been amended to clarify the claimed method as one in which the method is to enhance transport of a compound through a lipid bilayer, such as a cell wall, by complexing the compound with a diketopiperazien. Claim 22 has been amended to define the method of claim 14, wherein the molecular weight of the compound is less than 50 kDa. Support for the amendment can be found in the specification at least at page 8, line 23.

Rejection Under 35 U.S.C. § 102

Claims 1-36 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,071,497 to Steiner, et al. ("the '497 patent") and claims 1-7, 11-27 and 34-36 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,652,885 to Steiner, et al. ("the '885 patent"). Applicants respectfully traverse this rejection.

The Claimed Invention

The claims are drawn to a process to enhance transport of a molecule. This is achieved through complexation of the molecule with a diketopiperazine. The data in the examples establishes that the diketopiperazine does not induce an immune response (T or B cell immunity, see example 1), nor does complexing the diketopiperazine with the compound result in antibodies being formed to the compound (example 1, figure 11). However, complexation does result in enhancement of transport systemically (example 2, figures 3a and 3b, 4, and 10) and into specific cells (example 3, figure 5). Example 8 shows that the enhancement is not specific to a particular diketopiperazine. Example 9 shows that the enhanced transport is not prevented by crosslinking of cell membrane receptors.

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to make and use the invention. "A claimed invention cannot be anticipated by a prior art reference

if the allegedly anticipatory disclosures cited as prior art are not enabled". *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003).

The Prior Art

The '497 Patent

The '497 patent describes a drug delivery system comprising a complex of diketopiperazine and drug to be delivered. The complex is formed by co-precipitation or absorption of the drug to the diketopiperazine. This complex is then lyophilized to form a dry powder suitable for pulmonary administration.

In contrast to the '497 patent, the claims of the present application define a method for enhancing transport of a compound across a membrane or lipid bilayer.

Nowhere in the '497 patent is there any teaching that complexation with diketopiperazine can enhance transport through a lipid bilayer. The '497 patent describes a pulmonary formulation which is administered as dry powder particles to the lung. The lung is lined with a layer of mucosa, so the particles initially contact the mucosa, ***not*** the underlying cell membranes. Second, there is no indication in the '497 patent that uptake will be enhanced by the diketopiperazine, only that there will be uptake - indeed, there is a suggestion that it will be adequate but less than that which occurs with injection of the same drug.

Since at least one of the claimed elements, enhancing uptake, in the independent claims is not present in the reference, the reference cannot anticipate. To the extent the examiner is arguing that the lack of immune response is an inherent outcome of the use of the prior art composition, it is well established that the mere possibility something may occur is not

sufficient. It must be a definite and predictable outcome of what is disclosed. This simply cannot be concluded based on what is disclosed by the '497 patent.

There is certainly no recognition in the '497 patent of how much uptake will be enhanced, nor that it will not elicit an immune response, nor that a defined schedule of administration should be followed, as defined by the dependent claims in the present application (which the examiner seems to have overlooked, the rejection being made under 102(b).

Therefore, the '497 patent does not disclose, nor make obvious, the claimed method and claims 1-36 are not anticipated by the '497 patent.

The '885 patent

The '885 patent describes a method for purifying peptides and proteins by incorporating them into diketopiperazines to facilitate removal of one or more impurities.

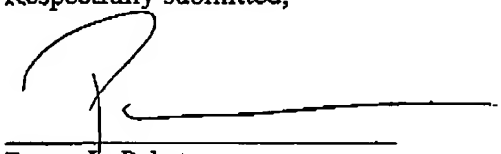
The '885 patent does not disclose or suggest a method for enhancing transport of a compound across a membrane or lipid *bilayer* or contacting the proximal face of a membrane or bilayer with a diketopiperazine-drug complex. The '885 patent does not disclose or suggest that the compound can be transported through a lipid bilayer faster in the presence of diketopiperazine that in the absence of diketopiperazine. The '885 patent describes a microparticle formulation containing drug and diketopiperazine administered via inhalation to the lungs. As discussed above, the lung is lined with a layer of mucosa, so the dry powder particles initially contact the mucosa, not the underlying cell membranes.

As noted above, the defined schedules of administration are not disclosed by, nor obvious in view of, the cited reference.

There is also no recognition in the '885 patent that the diketopiperazine-drug complex will not elicit an immune response nor that a defined schedule of administration should be followed, as defined by the dependent claims in the present application. Therefore, claims 1-36 are not anticipated by, nor obvious in view of, the '885 patent.

Allowance of claims 1-36 is respectfully solicited.

Respectfully submitted,



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